REMARKS

Claims 66-75, 111 and 113-133 were pending. Claims 66, 67, 69, 122, 124 and 127-129 have been amended to include periods, as requested in the *Office Action*. Claim 71 has been amended to recite more precisely the step of imaging the compound after administration of the compound to the patient. Claim 111 has been amended to recite the steps of synthesizing D32. Support for this amendment can be found throughout the disclosure of the present invention, *e.g.*, in the Specification, Example 9.

Claim 125 has been amended to delete an erroneously inserted structure, which is already present in claim 128 and was inadvertently duplicated in claim 125.

New claim 134 has been added. This claim recites the steps of synthesis of D33. Support for this new claim can be found throughout the disclosure of the present invention, *e.g.*, in the Specification, Example 9.

The Specification has been amended to include a reference to copending Application No. 10/382,082, to delete an inadvertently duplicated reference to that same Application, and to delete an inadvertently duplicated Sheme directed to the synthesis of D32. No new matter has been added.

Claims 66-75, 111 and 113-134 are now pending.

I. Double Patenting Rejections

Claim 67 has been rejected under the judicially created doctrine of obviousness-type double patenting as purportedly being unpatentable over claims 3 and 57 of copending Application No. 10/379,287 ("the '287 application").

Presently pending claim 67 is directed to dimer D33. However, contrary to the Examiner's statement, claims 3 and 57 of the '287 application are not directed to a D32 dimer. Therefore, given the Examiner's position that all of Applicants' other dimers are distinct inventions (*i.e.*, the present 81-way restriction requirement), Applicants respectfully request clarification or withdrawal of this rejection.

II. Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 74 and 75 have been rejected under 35 U.S.C. § 112, ¶ 1, as purportedly failing to comply with the enablement requirement. Applicants respectfully disagree and submit that claims 74 and 75 are indeed fully enabled under 35 U.S.C. § 112, ¶ 1.

The standard for determining whether the claims are enabled is whether one skilled in the art can practice the invention without undue experimentation. MPEP § 2164.01. Thus, the relevant question is whether one skilled in the art can practice the claimed methods for treating disease comprising the recited step without undue experimentation. Applicants respectfully submit that the answer is in the affirmative – one skilled in the art can indeed practice the claimed methods of treating disease without undue experimentation by implementing the recited steps in claims 74 and 75.

Claim 74 is directed to a method of treating a disease, comprising the step of administering to a patient a pharmaceutical preparation comprising a compound of claim 66 or 67. Claim 75 is directed to a method of treating a disease associated with angiogenesis, comprising the step of administering to a patient a pharmaceutical preparation comprising a compound of claim 66 or 67.

One skilled in the art would understand which diseases these include and, as explained below, would be able to practice the claimed methods of treating without undue

experimentation. Indeed, to supplement the skilled artisan's knowledge, the instant Specification provides a list of diseases associated with angiogenesis, other diseases that can be treated with the invention, as well as information about administration of the compounds for treatment, assessing efficacy, etc. of such diseases, *e.g.*, at pages 52-56 and 85-86. It should also be noted that the recited diseases include a number of the diseases that the Examiner has conceded are enabled, *e.g.*, in the *Office Action*, pages 6-7).

Because claims 74 and 75 are directed to methods of treating disease, the claims are therefore fully enabled. Simply put, one skilled in the art would know what qualifies as a "disease." One skilled in the art would also know how to administer the claimed compounds. One skilled in the art would further know whether the administration of the claimed compound results in the disease's becoming better or worse. As such, one skilled in the art can readily practice the claimed invention without undue experimentation.

Additionally, a review of the eight (8) *Wands* factors confirms that the present invention is fully enabled:

1. Nature of the Invention

   The present claims are directed to multivalent constructs, specifically D32 and D33, that are useful for, *inter alia*, diagnostic and therapeutic applications. These applications include methods for treating a disease with the claimed compounds, and particularly for treating diseases associated with the target to which the claimed compounds localize.

2. State of the Prior Art

It is well known in the art what a "disease" is. It is further well known in the art how to monitor a disease during treatment to see whether the treatment for that disease is working or not. Furthermore, the association of diseases with a variety of targets is known to the skilled artisan.

3. The Level of One of Ordinary Skill in the Art

A person skilled in the art would be a scientist with an undergraduate degree in chemistry or biochemistry and at least two years of postgraduate research or work experience in the field of diagnostic and therapeutic agents. The *Office Action* states that the present Specification "does not enable the public to use the compounds of the claimed invention in such a vast number of diseases." (p. 6). However, the standard is whether one of ordinary skill in the art would be able to practice the claimed invention without undue experimentation. Applicants respectfully submit that the answer to that question is yes.

4. Level of Predictability in the Art

The art, as it pertains to determining whether a disease is responding to a treatment or not, is very predictable and well known. Thus, there is no undue experimentation involved in practicing the methods of claims 74 and 75.

5. Amount of Direction and Guidance Provided by the Inventor

The Specification provides general guidance that the claimed compounds may be used to treat diseases by administering them. The

Specification teaches that "where binding of a protein or other molecule (*e.g.*, a growth factor, hormone, etc.) is necessary for or contributes to a disease process and a binding moiety inhibits such binding, heteromultimers including such binding moieties may be useful as therapeutics. Similarly, where binding of a binding moiety itself inhibits a disease process, heteromultimers containing such binding moieties may also be useful as therapeutics." Specification, page 84, lines 19-24. *See also* page 51, lines 20-22 ("a compound of the invention that inhibits a biological process that contributes to a disease state may itself be used as a therapeutic or pharmaceutical composition"). The Specification further explains that the compounds of the invention are particularly effective at treating diseases associated with the target, receptor, etc. to which the compounds localize, and, to supplement the knowledge of the skilled artisan, also provides an extensive list of such diseases as well as methods of administering the compounds for treatment, assessing efficacy, etc. *See*, *e.g.*, pages 52-56 and 85-86. In sum, the Specification provides significant guidance allowing the skilled artisan to practice the claimed methods without undue experimentation.

6. Existence of Working Examples

No examples need to be provided in order to establish that the invention is adequately described. MPEP § 2164.02 ("Compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed"). This is especially true where

the present Specification discloses the invention in such a manner that one skilled in the art will be able to practice the claimed invention without any undue experimentation. Nevertheless, the Specification does provide specific working examples, *e.g.*, Example 29.

7. Breadth of Claims

Claim 74 is directed to a method of treating a disease, comprising the step of administering to a patient a pharmaceutical preparation comprising a compound of the present invention. Claim 75 is directed to a method of treating a disease associated with angiogenesis, comprising the step of administering to a patient a pharmaceutical preparation comprising the compounds of the present invention. The *Office Action* contends that the claims are broad, and therefore are indefinite because of the "vast number of possible diseases known to exist which may be used in combination with the compounds of the present invention." (*Office Action*, p. 7). However, Applicants further note that breadth of a claim should not be equated with indefiniteness. MPEP 2173.04. As such, the statement that many "[t]he claims encompass a vast number of possible diseases" is not applicable for an enablement analysis. As explained in **Section II**, *supra*, claims 74 and 75 are definite and clear.

8. Quality of Experimentation Needed to Make Or Use the Invention Based on the Content of the Disclosure

Contrary to the assertions of the *Office Action*, there is no need or requirement to describe all of the possible diseases that can be treated with

Applicants' claimed composition. Rather, all that is required is that one skilled in the art be able to treat a disease by following the recited administration step without undue experimentation. Because the Specification teaches one skilled in the art how to make and use the claimed compounds, and because it is well known in the art how to administer compounds to a patient and how to determine whether a disease is responding to the administered compound (and the instant Specification supplements this knowledge as indicated above), no undue experimentation is needed to practice Applicants' claimed method for treating a disease by administering to a patient a pharmaceutical composition comprising the claimed compound. In other words, one skilled in the art is able to treat disease as recited in claims 72-74 and 76, simply by administering the claimed compositions to a patient.

As the analysis of the *Wands* factors confirms that there is no undue experimentation required to practice the invention, withdrawal of this rejection is respectfully requested.

III. Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 66-75, 111 and 113-133 have been rejected under 35 U.S.C. § 112, ¶ 2, as purportedly being indefinite. Applicants respectfully traverse, and will address the rejection of each of the claims in turn.

Claims 66, 67, 69, 122, 124, 125 and 127-129: These claims were rejected as purportedly missing periods. Claim 125 has been amended to delete a structure that was

inadvertently recited. As requested, Applicants have herein amended the remaining rejected claims to include a period at the end of each claim. Therefore, Applicants respectfully submit that the rejection of these claims has been overcome, and furthermore that the rejection of claims 68-75 and 113-133 (which depend therefrom) have also been overcome, and should be withdrawn.

Claims 66 and 67: The rejection of these claims is not understood. The structure recited in claim 66 is D32, and the structure recited in claim 67 is D33. This is supported in the Specification at, *e.g.*, p. 173 (structure of D32) and p. 174 (structure of D33). To further clarify this, claim 67 has been amended to include the caption "D33" below the structure. Therefore, withdrawal of this rejection is respectfully requested.

Claim 71, line 5: Claim 71 has been amended to recite more precisely the step of "imaging the compound after administration of the compound to the patient." Therefore, Applicants respectfully submit that this rejection has been overcome and should be withdrawn.

Claim 111: As requested, Applicants have amended claim 111 to incorporate the structure of D32 into the claim, and additionally to recite the steps of synthesizing D32. Support for these steps can be found in the Specification, *e.g.*, Example 9.

Further, Applicants have amended the present claim to add new claim 134, which recites the structure of D33 and the steps of synthesizing D33. Support for these steps can be found in the Specification, *e.g.*, Example 9.

As stated previously, Applicants believe that the structure of D32 was in fact correctly recited in claim 66, and that the structures of D32 and D33 are clear from the claims. Therefore, Applicants respectfully submit that this rejection has been overcome and should be withdrawn.

Claims 119 and 132: These claims are purportedly ambiguous because of the term "derivative." Applicants respectfully submit that this term as used in the present claims is definite under 35 U.S.C. § 112, second paragraph. One of ordinary skill in the art would know the meaning of the "derivative" of a given compound, because the term "derivative" is a well known and well defined chemical term that is understood by any person working in the chemical or biological industry.

Specifically, one of ordinary skill in the art would understand the meaning of the term "diethylenetriamine pentaacetic acid, tetraazacyclododecane triacetic acid, or a carboxymethyl-substituted derivative thereof," as recited in claim 119, to refer to compounds that have retain the chelating ability of the enumerated compounds, and include, *e.g.*, the compounds recited in the Specification, p. 57, lines 1-25.

Similarly, one of ordinary skill in the art would understand the term, "polyethylene glycol derivative," as recited in claim 132, to refer to compounds that are useful as linkers and retain the characteristics of polyethylene glycol that make it useful as a linker for the present invention. In fact, contrary to the statement in the *Office Action*, "which portion of the parent structure remains in the derivative" is irrelevant.

Additionally, a search of the USPTO patents database reveals over 10,000 patents whose claims include the word "derivative" in the context of chemical compositions, indicating its frequent use and acceptance by the USPTO. Therefore, Applicants respectfully submit that the term "derivative" is definite.

Claim 123, lines 10-11: The phrase, "a homopolyamide or heteropolyamide derived from synthetic or naturally occurring amino acid" is clear and understood in the art to define a group of organic compounds that contain more than one of either the same or different

amine groups as well as carbon, nitrogen, or hydrogen, and which are derived from amino acids that are either synthesized or naturally occurring. As the meaning of synthesized or naturally occurring amino acids is clear, and the meaning of compounds derived from them is clear, homopolyamines and heteropolyamines derived from them are also clear and definite. Therefore, Applicants respectfully submit that the rejection of this claim under 35 U.S.C. § 112, ¶ 2 should be withdrawn.

Claim 133: The terms "bioactive agent," "a cytotoxic agent," "a drug," "a chemotherapeutic agent" and "a radiotherapeutic agent" have been objected to as ambiguous. Applicants respectfully submit that one of ordinary skill in the art would understand the meaning of these terms, particularly in view of the discussion in the Specification: "As used herein the term "therapeutic" includes at least partial alleviation of symptoms of a given condition." (Specification, p. 88). Furthermore, the Specification explains that "[t]he terms "therapeutic agent" or "therapeutic" refer to a compound or an agent having a beneficial, therapeutic or cytotoxic effect in vivo. Therapeutic agents include those compositions referred to as, for example, bioactive agents, cytotoxic agents, drugs, chemotherapeutic agents, radiotherapeutic agents, genetic material, etc." (*Id.* at p. 27).

The term "bioactive agent" is known to a skilled artisan to refer to an agent that interacts with a target in an organism (or a component thereof) to produce a desired effect, such as, for example, providing information about the target or inducing a biological effect. Additionally, a search of the USPTO patents database reveals over 350 issued patents with claims that contain the term "bioactive agent," in the context of chemical compositions, indicating its frequent use and acceptance by the USPTO.

The term "a cytotoxic agent" is known to a skilled artisan to refer to an agent that directly or indirectly causes the death of a cell. The present Specification further explains,

> HGF also protects against DNA-damaging agent-induced cytotoxicity in a variety of cell lines susceptible to hyperproliferative phenotypes (*e.g.*, breast cancer). Therefore, preventing HGF from binding to cMet could predispose certain cancer cells to the cytotoxicity of certain drugs.

Specification, p. 7, lines 3-6.

The term "a drug" is well known to a skilled artisan to refer to a substance that when administered to an organism produces a desired beneficial effect.

The term "a chemotherapeutic agent" is well known to a skilled artisan to refer to an agent that is useful for at least partial treatment or alleviation of symptoms of a given condition, or production of a desired or beneficial effect, and may be useful for chemotherapy, particularly in treating cancer. Examples of chemotherapeutic agents are given on pages 81-82 of the Specification.

The term, "a radiotherapeutic agent" is well known to a skilled artisan to refer to an agent that comprises an unsealed source of radioactivity and is useful for at least partial treatment or alleviation of symptoms of a given condition, or production of a desired or beneficial effect, and may be useful for radiotherapy.

Because of these terms are clear and definite to a skilled artisan, Applicants respectfully submit that they are definite.

IV. Objections to the Specification

The Specification has herein been amended to recite the correct application serial number for copending application U.S.S.N. 10/382,082, entitled "KDR and VEGF/KDR binding peptides and their use in diagnosis and therapy."

CONCLUSION

In light of the above amendments and remarks, Applicants respectfully submit that the claims are in condition for allowance, early notice of which is earnestly sought.

If any outstanding issues remain, the Examiner is invited to telephone Applicants' undersigned attorneys at her convenience at the number provided below.

No fees are believed due in connection with the filing of this *Amendment and Response to Office Action.* However, the Director is hereby authorized to charge any required fees and credit any overpayments to Deposit Account No. 50-0540.

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Respectfully submitted,

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